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Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional Specification filed on 13/05/2003 in respect of Patent Application No. 479/MUM/2003 of CADILA HEALTHCARE LIMITED, a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India.

This certificate is issued under the powers vested in me under Section 147(1) of the Patents Act, 1970.

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Dated this 19th day of May 2004.

(R.BHATTACHARYA)
ASST. CONTROLLER OF PATENTS & DESIGNS.

FORM 1

THE PATENTS ACT, 1970

APPLICATION FOR GRANT OF PATENT

(See Sections 5(2), 7, 54 and 135 and Rule 33A)

(1) We, **CADILA HEALTHCARE LIMITED,** a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India

(2) hereby declare –

(a) That we are in possession of an invention titled

A SIMPLE METHOD FOR THE PREPARATION OF OMEGA FORM OF GATIFLOXACIN

(b) That the PROVISIONAL Specification relating to this invention is filed with this application;

(c) That there is no lawful ground of objection to the grant of a patent to us.

(3) Further declare that true and first inventors for the said invention are ,

(a) **VAKIL, Manish Harshadbhai**
(b) **PATEL, Satyen Gopalbhai**
(c) **LAKKAD, Mahendra Gordhanbhai**
(d) **NAIK, Ashish Prafullchandra**
(e) **AGARWAL, Virendra Kumar**
(f) **PANDITA, Kanwal**
(g) **PATEL, Pankaj Ramanbhai**

All Indian citizens, of R&D Center, Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India

(4) We claim priority from the application(s) filed in the following convention country(ies), particulars of which are as follows: **NIL**

479/MUM/2003
13/5/2003

(5) That we are the assignees of the true and first inventors,

(6) That our address for service in India is as follows;

SUBRAMANIAM, NATARAJ & ASSOCIATES
Attorneys-at-Law
Patent and Trademark Attorneys
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13/5/03

(7) Following declaration was given by the inventor

We, **VAKIL, Manish Harshadbhai; PATEL, Satyen Gopalbhai; LAKKAD, Mahendra Gordhanbhai; NAIK, Ashish Prafullchandra; AGARWAL, Virendra Kumar; PANDITA, Kanwal** and **PATEL, Pankaj Ramanbhai,** all Indian citizens, of R&D Center, Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India

the true and first inventors for this invention declare that the applicants herein are our assignees.

Manish Harshadbhai VAKIL

Satyen Gopalbhai PATEL

Mahendra Gordhanbhai LAKKAD

Ashish Prafullchandra NAIK

Virendra Kumar AGARWAL

Kanwal PANDITA

Pankaj Ramanbhai PATEL

(8) That to the best of our knowledge, information and belief the facts and matters stated herein are correct and there is no lawful ground of objection to the grant of patent to us on this application.

(9) Following are the attachments with this application:
- (a) PROVISIONAL specification in triplicate
- (b) Statement and Undertaking on FORM 3 in duplicate
- (c) Form 2 in triplicate

Fee Rs. ..... in Cash/Cheque/Bank Draft Bearing No..... dated.....on .....Bank.

We request that a patent be granted to us for the said invention.

Dated this 12th day of May 2003.

The Controller of Patents
The Patent Office,
At Mumbai

for CADILA HEALTHCARE LIMITED
(name and designation of signatory)

FORM 2

The PATENTS ACT, 1970

(39 of 1970)

Provisional Specification

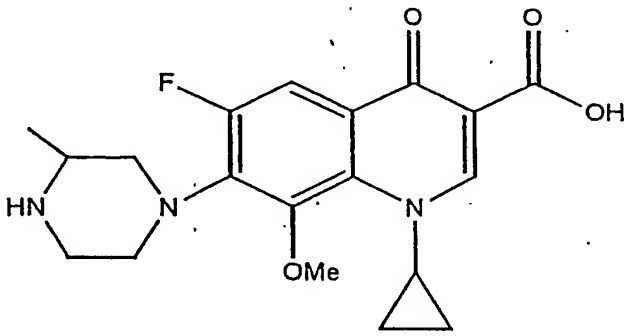
A simple method for the preparation of omega form of Gatifloxacin.

CADILA HEALTHCARE LIMITED, ZYDUS TOWERS, SATELLITE CROSS ROADS, AHMEDABAD 380 015, Gujarat, India

The following specification describes the nature of the invention:

SIMPLE METHOD FOR THE PREPARATION OF OMEGA FORM OF GATIFLOXACIN

The present invention discloses a novel process to manufacture mega form of Gatifloxacin. Gatifloxacin, chemically 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-3-guinodine carboxylic acid is represented by the following structural formula (I)



(I)

It is a broad-spectrum quinoline antibacterial agent. US 4980470, US 4997943, US 5043450, EP 230295 discloses the preparation of gatifloxacin. US 5860283, US 6413919 disclose 12 different crystalline forms of gatifloxacin and an anhydrous omega form.

Main aspect of the embodiment is to present a new process for the preparation of anhydrous-omega forms of gatifloxacin.

Other aspect of the embodiment is to provide and economical process for the purification of gatifloxacin.

During working on purification of gatifloxacin, it was found that our material is identical with omega form mentioned in the prior art references, wherein it is prepared by heating hemihydrate or pentahydrate above 170°C.

The preparation of omega form of anhydrous Gatifloxacin as disclosed in prior arts by heating hemihydrate or pentahydrate suffers the major disadvantage of degradation of the product and moreover the process for large scale preparation is not economical as well as is not recommended.

Through our experimentation, it has now been found that for the preparation of omega form of anhydrous Gatifloxacin heating at 170°C is not

necessary. It can be formed by crystallization from a suitable solvent at a relatively lower temperature.

In the literature (US 4980470, US 5043450) gatifloxacin is purified by adsorbing it in silica-gel column and eluting with chloroform: Methanol: Conc. Aqueous ammonia (20 : 6 : 1) and then crystallization from methanol. The operations as described above are not practical for the large-scale preparations.

The present invention provides a novel process to manufacture Gatifloxacin (1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-3-guinodine carboxylic acid) having structural formula (I) is disclosed. The invention does not require high temperature or use of column chromatography for purification. Moreover the solvents being used in the process can be recovered and recycled. These factors make the process industrially efficient.

This is a tedious process. This hurdle has been overcome by providing a novel, inventive and simple process for the preparation and purification of Gatifloxacin, which eventually gives omega form of anhydrous Gatifloxacin.

a) Prior art discloses the condensation of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid with 2-methylpiperazine in dimethyl sulfoxide. Dimethyl sulfoxide is removed by vacuum distillation and the residue is purified by silica gel column chromatography. This process is not economical/ practical on plant scale.

b) To overcome the disadvantages Gatifloxacin crystallization is achieved after the reaction is over by diluting dimethyl sulfoxide reaction mixture with isopropanol and the product is collected by filtration and also dimethyl sulfoxide distillation is removed.

c) Crude Gatifloxacin obtained by above procedure is taken in methanol containing potassium hydroxide, resulting via clear solution. The pH of the solution is then neutralized to 7 to 7.5 by acetic acid resulting in precipitation of Gatifloxacin. The precipitated Gatifloxacin is then heated to reflux temperature for 30 to 60 minutes. The product is then cooled to 5 to 10^{o}C and is then filtered and is dried at 70 to 75 ^{o}C for

20 hours. The water content at this stage is less than 1% and DSC and X-Ray powder diffractogram confirm the nature of product as omega form of anhydrous Gatifloxacin. However residual methanol content in the product is higher than allowable limits of 3000 ppm.

d) To overcome the problem of high residual methanol content, the dried product is refluxed in either of the following solvents

(i) Methanol

(ii) Aqueous methanol (5 - 10 %)

(iii) Methanol with 50% removal of solvent at atmospheric pressure

(iv) Cyclohexane

(1) Gatifloxacin so obtained is heated to reflux temperature with methanol for 1 hour and is then cooled to 5°C to 10°C. The product is collected by filtration and is dried for 35 hours at 70 to 75°C. DSC and X-ray powder diffractogram confirm the nature of the product as omega form of anhydrous Gatifloxacin with methanol content 300 - 500 ppm.

(2) Gatifloxacin thus obtained with higher residual methanol content is refluxed with aqueous methanol (5 - 10 %) for 1 hour and is then cooled to 5°C to 10°C. The product is collected by filtration and is dried for 35 hours at 70 to 75°C. DSC and X-ray powder diffractogram confirm the nature of the product as omega form of anhydrous Gatifloxacin with methanol content 300 - 500 ppm.

(3) Gatifloxacin thus obtained with higher residual methanol content is refluxed with 10 volumes of methanol, 50% of methanol is then removed by distillation at atmospheric pressure. The mass is then cooled to 25 to 30°C. The product is collected by filtration and is dried for 24 hours at 70 to 75°C. DSC and X-ray powder diffractogram confirm the nature of the product as omega form of anhydrous Gatifloxacin with methanol content 300 - 500 ppm.

(4) Gatifloxacin thus obtained with higher residual methanol content is refluxed with cyclohexane, Methanol and traces of water are removed by azeotropic distillation using Dean Stark apparatus. The mass is then cooled to 25 to 30°C. The product is collected by filtration and is dried for 15 hours at 70 to 75°C. DSC and X-ray powder diffractogram confirm

the nature of the product as omega form of anhydrous Gatifloxacin with cyclohexane content 1600-1900 ppm and methanol content 5 – 10 ppm.

All the above experiments reproducibly give omega form of anhydrous Gatifloxacin. DSC of all experiments exhibit a single peak at 191 to 192°C with a heating rate of 10°C per minute. The disclosed methods herein have the following advantages over the prior art processes.

1) Avoids column chromatography for purification.
2) Eliminates the heating of the product at high temperature above melting point.
3) A simple process of heating with methanol which can be performed on commercial scale.
4) Methanol and cyclohexane are recovered and recycled.

The invention is now described in detail:

1) 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid is reacted with 2-methylpiperazine in DMSO at 60-65°C for 42 hrs.
2) Then it is diluted with 1 to 10 volumes preferably 5 volumes of isopropanol based on DMSO used.
3) The product is collected by filtration and drying for 4 hours at 70-75°C giving crude Gatifloxacin.
4) This is purified by heating with 3 to 10 volumes, preferably 4 volumes of methanol as that of crude Gatifloxacin 1 to 2 mole equivalent preferably 1.2 mole equivalent of Potassium hydroxide resulting in the clear solution which is filtered through hyflow supercell.
5) The pH of the clear solution thus obtained is adjusted to 6 to 8 preferably 7 to 7.5 addition of acetic acid. Resulting in the precipitation of Gatifloxacin.
6) After the pH adjustment the slurry is refluxed for 1 hour.
7) Then it is cooled to 5 to 10°C
8) The product is collected by filtration, which is dried at 70-5°C for 20 hrs, The product thus obtained is identified as omega form of anhydrous Gatifloxacin.

In an another embodiment pure Gatifloxacin having moisture content 4.5% is treated with different quantities of methanol under different conditions.

(A) Gatifloxacin is heated at 40 to 70°C preferably to reflux temperature for 30 to 60 minutes with 5 to 20 volumes preferably 12.5 times of methanol, the product is filtered at 0 to 25°C; preferably at 5-10°C and drying at 50 to 100°C for 10 to 50 hrs preferably at 70-75°C for 30-35 hours gives Gatifloxacin having moisture content 0.24% w/v

(B) Gatifloxacin is heated at 40 to 70°C preferably to reflux temperature with 5 to 20 volumes preferably 12.5 volumes of methanol and 0.1 to 10 volumes, preferably 1 volume of deionized water and worked up as in method (A) gives product having water content 0.31% w/v.

(C) Gatifloxacin is stirred with 5 to 20 volumes preferably 10 volumes of methanol. 40 to 60% of methanol is distilled at atmospheric pressure, the product is recovered by filtration at room temperature, dried at 70-75°C for 24 hours.

(D) Gatifloxacin is refluxed with 5 to 10 times of cyclohexane, methanol and traces of water is removed by azeotrically using Dean-Stark apparatus. The product is isolated by filtration at 25 to 30°C and is dried at 70-75°C for 15 hours.

The invention will be illustrated in detail showing examples

Example 1:

Step A:

A mixture of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinoline carboxylic acid (100gm), 2-methylpiperazine (67.8gms) and anhydrous DMSO (300 ml) are stirred for 40-45 hrs at 60-65°C. The reaction mass is then diluted with 1500 ml isopropyl alcohol. It is then stirred 30 min at 25-30°C and filtered, & washed with 3 x 50 ml isopropylalcohol and dried for 4 hours at 70 to 75°C yield 71 gm.

Step B:

100 gm of the above product is dissolved into a solution of 400 ml methanol and 20 gm of potassium hydroxide, is filtered through hyflow and supercell washed with 2 x 20 ml of methanol. The pH of the filtrate is

adjusted to 7.0 –7.5 with acetic acid (20.4 ml). The mixture is then refluxed for 1 hr and is cooled to 5-10°C, is filtered, giving wash of 2 x 100 ml of methanol. The product is dried at 70-75°C for 20 hrs. Weight = 80 gm. Methanol content = 20000 to 30000 ppm. Water content = 0.38%

Example 2:

40 gm of gatifloxacin is heated to reflux at 65-70°C for 1 hr with 500 ml methanol. It then cooled to 5-10°C and stirred for 1 hr, filtered and washed with cold methanol (2x20 ml). It is dried at 70-75°C for 35 hrs. Weight= 37.5 gm, water content=0.24% w/w.

Example 3:

40 gm gatifloxacin is heated to reflux at 65-70°C for 1 hr with 500 ml methanol and 40 ml deionized water. Then it is cooled to 5-10°C and the temperature is maintained for 1 hr, filtered, washed with cold methanol (2x20 ml), dried at 70-75°C for 30-35 hrs.

Wt. = 38 gm, water content =0.31% w/w

Example 4:

20 gm gatifloxacin is stirred with 200 ml of methanol. 100 ml of methanol is distilled at atmospheric pressure. It is cooled to 25-30°C and filtered, gave wash of methanol (2x10 ml). Dried at 70-75°C for 24 hrs.

Wt. 19 gm , water content =0.38% w/w.

Example 5:

100 gm gatifloxacin and 200 ml of cyclohexane are refluxed. Methanol & traces of water are removed azeotropically by dean stark apparatus. Then cooled to 25-30°C and filtered dried at 70-75°C for 15 hrs.

Wt. 94 gm, water content = 0.38% w/w

Confirms anhydrous omega form by XRD.

While work is still underway to complete the invention, it must be understood that the above description is illustrative and not limiting of the scope of the invention.

Dated this the 12th day of May 2003.

G NATARAJ
Of Subramaniam, Nataraj & Associates
Attorneys for the Applicants